Testosterone and Sexual Function

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KEYWORDS

• Testosterone replacement therapy • Sexual dysfunction • Erectile dysfunction • Hypogonadism • Libido • Ejaculatory function

KEY POINTS

- Sexual and erectile dysfunction are common conditions, becoming more common as men age. Hypogonadism frequently occurs concurrently with erectile dysfunction.
- The current literature seems to show a beneficial effect on sexual symptoms/function of testosterone replacement therapy (TRT) in the setting of hypogonadism.
- TRT may improve a patient's response to a phosphodiesterase inhibitor.
- Other forms of TRT seem to show a similar response, with improvement of sexual function in limited studies.

INTRODUCTION

Although "testosterone" is synonymous with "sexual function" in the lay media, the actual role of endogenous testosterone levels and the use of exogenous testosterone to predict or treat sexual dysfunction, respectively, is not clear. Testosterone levels and replacement have been linked with sexual function, specifically erection quality, libido, and ejaculatory function in a variety of studies.

To what extent serum testosterone testing is performed as a result of men presenting with complaints of sexual dysfunction is not entirely clear, despite the European Male Aging Study (EMAS), which showed a clear relationship between sexual symptoms and biochemical hypogonadism. This 2010 study conducted at 8 European centers showed a clear relationship between decreased frequency of morning erections, decreased frequency of sexual thoughts, erectile dysfunction, and serum total and free testosterone levels.[1] This study further showed an increase in symptoms correlating to declining testosterone levels.[1]

Erectile dysfunction is common and the proportion of men experiencing erectile dysfunction is expected to increase as the US population ages. It is projected that more than 35 million American men will experience erectile dysfunction, effecting up to 50% of men by age 50.[2] According to the EMAS, 30% of European men experienced erectile dysfunction; however, only 17% of these men were found to have low serum testosterone (<11 nmol/L) with proper testing.[1]

The screening for hypogonadism and subsequent testosterone treatment has continued to grow in the United States and worldwide.[3] A recent study showed this growth is not solely limited to older men, with evidence suggesting that testosterone prescriptions have nearly tripled in men in their 40s.[4] Based off estimates, testosterone prescriptions have grown from a $300 million dollar industry in 2002 to a more than $2 billion dollar industry in 2013.[5]

Penile erection is a complex process involving the interplay between penile vasculature, neural impulses, the hormonal milieu, and cognitive behavior.[6] Erectile dysfunction is among the

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most common forms of sexual dysfunction, but other disorders such as decreased libido, ejaculatory disorders, and orgasmic dysfunction have a role in sexual dysfunction.[7]

Testosterone therapy has been shown to have an impact on sexual function in several studies; however, lack of standardization of sexual function assessment between studies has made their results difficult to interpret.[7] Guidelines for screening and treatment provided by multiple societies diverge regarding testosterone replacement and treatment of sexual dysfunction adding to even greater confusion among health care providers.[3,8,9]

As an example, the most recent Endocrine Society guidelines seek to differentiate androgen deficiency and erectile dysfunction as 2 independent disorders with separate etiologies that may coexist.[3] This assertion contrasts with the current European Association of Urology and other guidelines, which suggest that hypogonadism is a reversible cause of erectile dysfunction.[8,9] Regardless of this distinction, it seems that testosterone plays at least some role in the maintenance and perhaps enhancement of sexual function. This, combined with the increase in testosterone prescriptions, suggests that knowledge of the evidence both for and against the use of testosterone to treat sexual dysfunction is critical for all health care providers practicing in this clinical arena.

The goal of this article is to explore some of the current studies regarding testosterone replacement therapy (TRT) and its relation to sexual function.

PATHOPHYSIOLOGY

The impact of testosterone on male sexual function is not surprising. Several anatomic studies have revealed that androgen receptors are densely expressed in the male genital tract, the spinal nucleus, the medial preoptic area of the hypothalamus, and the bulbocavernosus muscle.[10,11]

In the central nervous system, specifically the medial preoptic area within the hypothalamus, androgens exert an influence on the release of several stimulatory neurotransmitters, including dopamine, oxytocin, and nitric oxide.[12] These neurotransmitters are not only related to sexual arousal and erection in mature subjects, but are also responsible for the control of sexual development in adolescence.[12]

In addition to their role in the central nervous system, androgens seem to be involved in the control and modulation of trabecular smooth muscle, endothelium, and fibroelastic properties of the corporal bodies.[12,13] In studies of castrated animals, the absence of circulating androgens leads to lower nitric oxide synthase activity, leading in turn to a decrease in vasodilation and erectile function. The absence of androgens may also lead to a disruption of smooth muscle relaxation and contraction in the nonadrenergic noncholinergic (NANC and α1-adrenergic pathways) associated with smooth muscle contraction within the sympathetic nervous system.[14,15]

However, not all studies have had consistent findings with regard to the role of androgens in sexual development and function. In an apparent contradiction to the findings discussed, several other animal studies have suggested that the variable regulation of the enzyme phosphodiesterase in the setting of hypogonadism may effectively compensate for the loss of androgen, thus leading to erectile preservation.[16] Importantly, these studies seem to be species dependent, and their extrapolation to human function should be guarded.[14–16]

A decrease in serum testosterone has been linked to increased connective tissue deposition within the erectile bodies and a subsequent decline in penile elasticity and overall erectile quality.[17]

ERECTILE FUNCTION

Penile erection is a complex interplay between neurologic and vascular pathways. Erectile function may be impacted negatively by vascular insults, including hypertension, hyperlipidemia, and atherosclerosis.[8] Erectile function additionally may be impacted by endocrine disorders such as diabetes and hypogonadism.[8]

A number of clinical trials have been conducted to characterize the impact of testosterone treatment on erectile function, with inconsistent findings. In an effort to consolidate the available evidence, a recent metaanalysis evaluated the effect of TRT on various aspects of sexual function, including erectile function.[7]

This metaanalysis conducted by Corona and colleagues[7] in 2014 sought to identify all randomized controlled trials comparing the effect of TRT versus placebo on sexual function (which was further broken down by cause of dysfunction). They also sought in this study to compare the effect of TRT as a supplement to phosphodiesterase inhibitors on erectile function.

Within this larger metaanalysis, 24 studies that included 1473 patients met inclusion criteria examining erectile function. To be included, studies needed to compare testosterone treatment to placebo and assess erectile function through a variety of standardized (the International